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LETTERS AND CORRESPONDENCE

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Prolymphocytic Transformation in Chronic Lymphocytic Leukemia Presenting as Bilateral Periorbital Swelling

To the Editor: Several reports have documented cases of myeloid leukemias and myeloproliferative disorders associated with extramedullary myeloid cell tumor (EMT) [1]. We present a patient of chronic lymphocytic leukemia (CLL) who, after 2 years from its initial diagnosis, developed bilateral periorbital swelling. Fine needle aspiration cytology (FNAC) of the right periorbital swelling and the peripheral blood smear examination at this stage revealed prolymphocytic (PL) transformation in CLL.

In October 1995, a 63-year-old woman was detected to have leucocytosis on routine medical examination. Splenomegaly was 2 cm below the left costal margin. There was no lymphadenopathy. Complete blood counts showed hemoglobin (Hb) 12 g/dL, platelets 138×10^9/L, leucocyte count 22.0×10^9/L; differential: lymphocytes 92%, neutrophils 08%. Bone marrow examination revealed near complete replacement by morphologically mature lymphoid cells. Immunocytochemical evaluation revealed that the lymphocytes were positive for CD5, CD19, CD23, kappa light chains; these cells exhibited weak surface immunoglobulin expression. A diagnosis of B-cell CLL (with stable Rai stage II) was made. She was treated with chlorambucil and prednisolone. Two years later in September 1997, she presented to our hospital with bilateral periorbital swelling, more prominent in the right eye (Fig. 1). There was no associated history of weight loss, fever, night sweats, or bleeding. Physical examination revealed hepatomegaly (2 cm) and splenomegaly (8 cm) below the right and left costal margins, respectively. There was no lymphadenopathy. Complete blood counts showed Hb 9.5 g/dL, platelets 80.0×10^9/L, leucocyte count 25.5×10^9/L; differential: prolymphocytes 72%, lymphocytes 20%, neutrophils 06%, monocytes 02%. Serum uric acid was 8.1 mg%. High resolution serum electrophoresis revealed a normal pattern. FNAC of the right periorbital swelling revealed a cellular aspirate showing lymphocytosis, including approximately 80% prolymphocytes. The prolymphocytes were bigger than twice the size of a lymphocyte, had low nuclear/cytoplasmic ratio, moderate amount of agranular blue cytoplasm, and round to oval nucleus with a prominent nucleolus (Fig. 2). Non-specific esterase and acid phosphatase cytochemistry were negative. Flow cytometric and immunocytochemical studies confirmed a monoclonal B-cell population of the prolymphocytes, which, in addition to CD5, CD19, CD23, and kappa immunoglobulin light chains, showed weak expression of CD22 and surface immunoglobulins, and lacked other T-cell markers. The remaining lymphocytes showed a similar expression. Immunophenotype and morphology were consistent with B-cell PL transformation in CCL. She was treated with cyclophosphamide, vincristine, and prednisolone but there was no clinical or hematological response.

Unlike de novo PLL, the immunophenotype of the prolymphocytes in PL transformation is similar to the classic B-CLL cells [2]. About 15% of

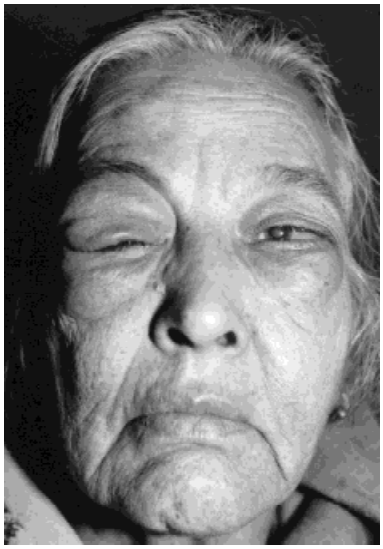

Fig. 1. Bilateral periorbital swelling, more prominent in the right eye.

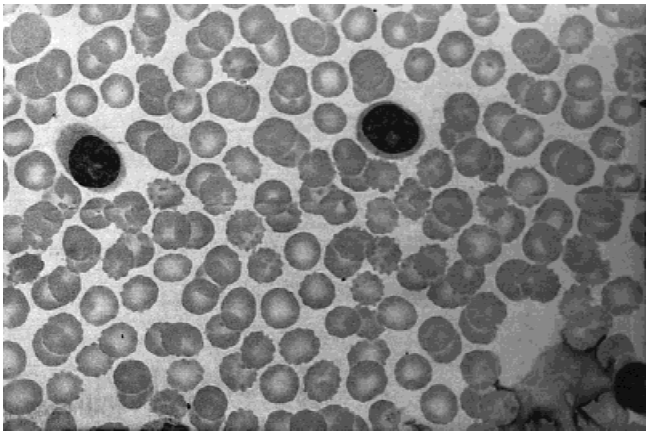

Fig. 2. Peripheral blood smear showing two prolymphocytes (Jenner Giemsa stain ×1,000).

B-cell CCL cases are designated as having CLL/PL (where PL are 10–50% of the total lymphoid cells) and 20% of these CLL/PL cases undergo PL transformation (>50% PL) [3]. Although extravascular involvement has been occasionally documented in de novo B-cell PLL [4], an association of PL transformation in CLL with soft tissue deposits has not been previously reported.

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Lymphoma With Multi-Gene Rearrangement on the Level of Immunoglobulin Heavy Chain, Light Chain, and T-Cell Receptor β Chain

To the Editor: In a recent report, Klein et al. [1] describe a patient with an axillary mass of diffuse mixed small and large cell non-Hodgkin's lymphoma (NHL), which responded well to conventional cytotoxic therapy and local irradiation. Immunophenotyping of the lymph node sample revealed ~35% T-lymphocytes and ~65% B-lineage cells with surface membrane expression of immunoglobulin μ heavy chain (IgM) in the absence of Ig light chains. Gene rearrangement studies showed multiple rearrangements in the *IGH, IGK,* and *IGL* genes as well as in the *TCRB* genes. The authors conclude from their immunophenotyping results that the malignant process concerned a precursor-B-malignancy of transitional-pre-B-cell type [1]. In our opinion, the lack of Ig light chain expression can be explained in a different way, i.e., as secondary loss of a functional Ig light chain rearrangement due to somatic hypermutation or to a chromosome aberration. This is in line with the observed *IGK* and *IGL* gene rearrangements. Furthermore, transitional-pre-B-cell malignancies are characterized by expression of the CD10 antigen and terminal deoxynucleotidyl transferase and such malignancies show a typical aggressive acute lymphoblastic leukemia (ALL) picture [2]. These characteristic clinical and immunophenotypic features were not present in the described patient with the intermediate-grade malignancy.

The authors conclude that the multiple rearrangement pattern of *IGH, IGK, IGL,* and *TCRB* genes in the lymph node cell population represents a multistep and multilineage neoplastic development that started in lymphoid stem cells. However, they do not provide conclusive evidence for the presence of more than one clonal cell population. In fact, the conclusion of multiple neoplasias is based on rearranged bands of different density, which might be caused by differential hybridization to rearranged restriction fragments, because of the usage of DNA probes that are (partly) complementary to gene segments that are involved in rearrangements or in chromosomal translocations [3,4]. Furthermore, the fact that *TCRB* gene rearrangements were detected as well, does not necessarily imply the presence of a clonal T-cell population. Cross-lineage TCR gene rearrangements are not restricted to precursor-B-ALL, but have also been reported in 2–10% of mature B-cell malignancies [5]. In a recently analyzed series of 60 B-NHL patients, we also found cross-lineage *TCRB* gene rearrangements in ~10% of cases (Van Krieken et al., unpublished results). The B-NHL origin of these *TCRB* gene rearrangements is illustrated in Figure 1 by a case of Ig lambda$^+$ extranodal B-NHL (T-cell markers negative) with a diffuse infiltrate (~90%) of malignant B-cells showing biallelic *IGH* rearrangements as well as a monoallelic (cross-lineage) *TCRB* gene rearrangement. In addition, clonal rearrangements were found in both *IGK* (Vκ-Jκ, Vκ-Kde) and *IGL* (Vλ-Jλ) loci.

In our opinion, the conclusion of Klein et al. [1] concerning an oncogenic event in lymphoid stem cells, which preceded the subsequent differentiation process into either B or T cell lymphoma, is too speculative. We would rather interpret their data as a case of Ig light chain negative mature B-cell lymphoma characterized by *IGH, IGK, IGL* as well as (cross-

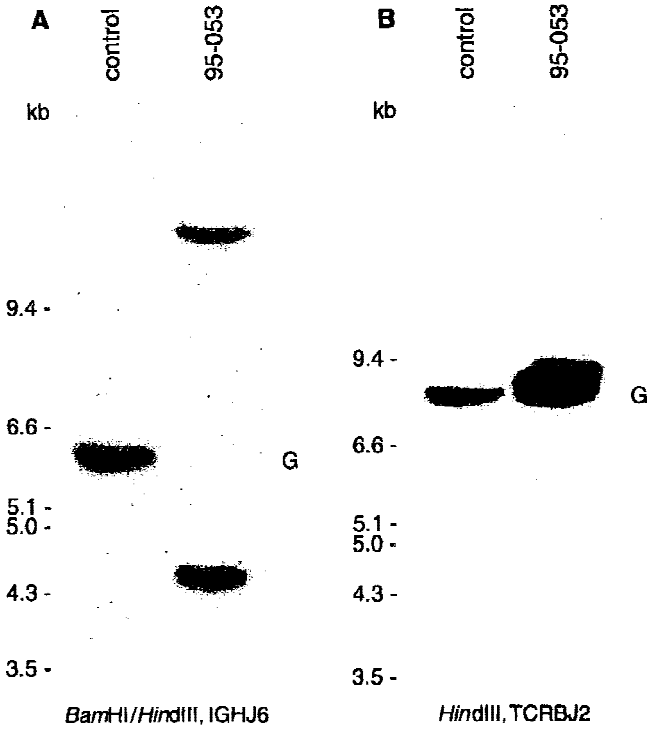

Fig. 1. A: Southern blot analysis of *IGH* genes. Control DNA and DNA from a B-NHL sample were digested with *Bam*HI/*Hin*dIII, size separated, and blotted onto a nylon membrane filter, which was hybridized with the ^{32}P-labeled IGHJ6 probe. Upon X-ray film exposure, biallelic rearrangements were found. Sizes (in kb) of the molecular weight marker are indicated. B: Control DNA and DNA from the same mature B-NHL sample were digested with *Hin*dIII. The filter was hybridized with the ^{32}P-labeled TCRBJ2 probe and a monoallelic rearrangement to the Jβ2 region of the *TCRB* genes was found.

lineage) *TCRB* gene rearrangements, which is accompanied by reactive T-lymphocytes.

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A Case of Idiopathic Hypereosinophilic Syndrome Complicated With Disseminated Intravascular Coagulation

To the Editor: Idiopathic hypereosinophilic syndrome (HES) represents a heterogenous group of disorders with common features of prolonged eosinophilia of undetectable cause and organ involvement [1]. Clinical manifestations are characterized by thromboembolic events of the involved organ, such as the heart, lungs, or nervous system. The most marked effect involves the heart and results in damage to the endocardium with subsequent thrombus formation and finally fibrosis, leading to restrictive cardiomyopathy [1]. Despite many laboratory findings that indicate eosinophilic augumentation of coagulation and fibrinolysis [2–5], few cases of systemic coagulation abnormalities have been reported [1,6]. We describe a patient with idiopathic HES complicated with disseminated intravascular coagulation (DIC) but without organ involvement.

A 17-year-old male with no previous illness complained of abdominal pain of unexplained cause in December 1997. Complete blood count on admission revealed: RBC, $531 \times 10^4/\mu l$, Hb, 14.2 g/dl; Ht, 41.0%; platelet, $4.3 \times 10^4/\mu l$; WBC, 11,900/μl (Neutro, 39.1%; Eo, 38.1%; Lymph, 13.5%; Mono 8.8%). Hemostatic study revealed; Prothrombin time 12.7 sec; partial thromboplastin time, 32.0 sec, fibrinogen, 442.3 mg/dl; fibrin degradation products (FDP), 37.9 μg/ml. The neutrophil alkaline phosphatase (NAP) score was 97.0% and serum antinuclear factor were negative. Bone marrow aspiration smear revealed hypercellular marrow with a myeloid to erythroid ratio of 6.32, and an increased number of mature eosinophil, 40%. Cytogenetic analysis of bone marrow cells revealed the karyotype of t(1;14)(q21;p1?) in all 20 cells analyzed. Chest X-ray was normal and

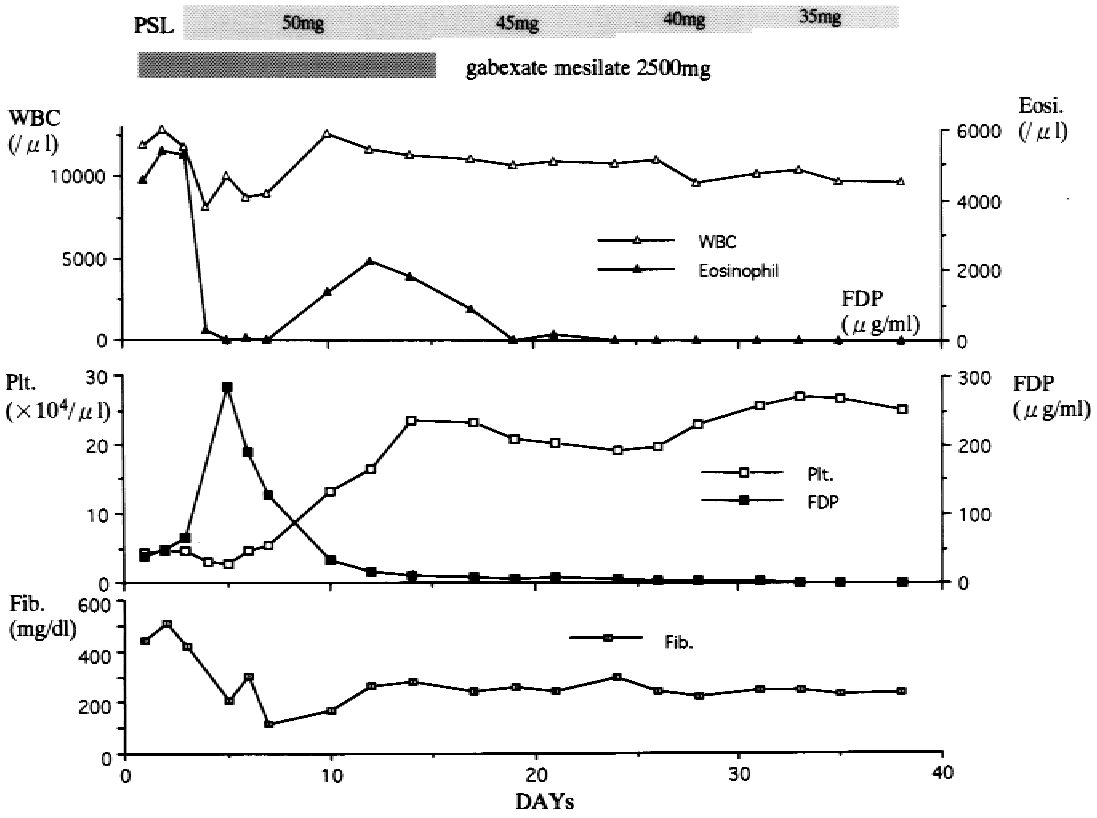

Fig. 1. Clinical course of the patient.

echocardiography showed normal cardiac performance. Plain abdominal roentgenograms showed gaseous dilatation of the small bowel suggesting ileus. No parasites or ova were found in the stool despite frequent examinations. Administration of gabexate mesilate, 2,500 mg/day, was started and prednisolone, 50 mg/day, was added on the third hospital day (Fig. 1) The patient complained of severe headache on the third hospital day and MRI revealed a small hemorrhagic infarction, one cm in diameter, at the right temporal lobe which was left untreated. Eosinophil counts decreased after administration of prednisolone and abdominal pain disappeared. The thrombocyte counts remained decreased, the fibrinogen level decreased, and FDP levels markedly increased shortly after the start of prednisolone administration. The thrombocyte counts, levels of fibrinogen, and FDP normalized after tapering the dose of prednisolone. DIC in the present case seemed to be caused by the increased eosinophils, since the patient had no underlying disease and DIC improved in proportion to decreased eosinophils in response to prednisolone.

Upon activation, eosinophils release four main granule proteins: major basic protein (MBP); eosinophi derived neurotoxin (EDN); eosinophi cationic protein (ECP); and eosinophil peroxidase (EPO) [1]. HES patients have high blood levels of ECP, and there are reports of enhanced factor-XII dependent reactions [2] and urokinase-induced plasminogen activation [3]. MBP and EPO activate platelets [4]. Local effects within the heart that promote thrombosis could be related to the capacity of MBP and ECP to bind to glycosylated thrombomodulin and to inhibit local anticoagulant activity to the endothelium [5]. A case of HES that required more heparin to achieve anticoagulation for cardiopulmonary bypass was reported [6]. In HES, not only the thromboembolic complications of the specific organs, but also the systemic alteration of coagulation should be examined.

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Interferon-Alpha Therapy for Chronic Myelogenous Leukemia During Pregnancy

To the Editor: Hydroxyurea or interferon-alpha (IFN-α) is effective in the treatment of chronic myclogenous leukemia (CML). However, the management of CML during pregnancy is a difficult problem because of the potential teratogenic effect of the therapy. We describe a patient with CML, treated with IFN-α during pregnancy, with an apparently successful outcome.

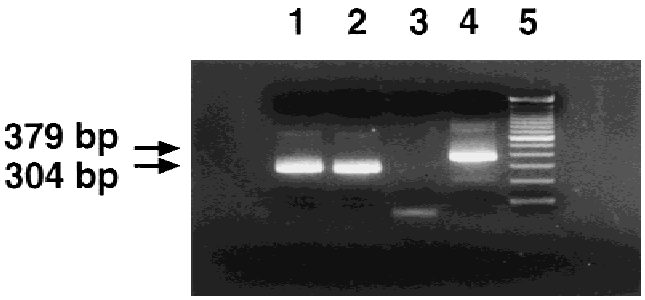

Fig. 1. PCR-amplified cDNA specific for the BCR-ABL transcript. Lane 1, maternal peripheral blood leukocytes at diagnosis (BCR exon 2—ABL exon 2 fusion, 304 base pairs); lane 2, maternal peripheral blood leukocytes at delivery; lane 3, cord blood; lane 4, the K562 cell line (BCR exon 3—ABL exon 2 fusion, 379 base pairs); lane 5, size markers.

A 23-year-old Japanese woman was diagnosed with Ph-positive CML when she was eight weeks pregnant. Subcutaneous IFN-α (Sumiferon, Sumitomo Seiyaku Co., Tokyo, Japan), three million units daily, was started during the 25th week (after informed consent was obtained) because of a rapid increase in her peripheral leukocyte count (99.2×10^9/L). This dose was increased subsequently to six million units daily during the 27th week. Throughout her pregnancy, ultrasonography showed a normal-appearing fetus. At 37 weeks gestation, the patient went into spontaneous labor and gave birth to a healthy male infant with a birth weight of 2,630 g, and Apgar scores of nine and 10 at one and five min, respectively. Physical examination revealed no congenital anomalies. The infant's blood counts and differential were all within the normal range for a neonate: White blood cell, 12.6×10^9/L; red blood cell, 4.51×10^{12}/L; hemoglobin, 16.0 g/dL; hematocrit, 45.5%; and platelet, 334×10^9/L. The postpartum period was uneventful. Reverse transcription (RT)-polymerase chain reaction revealed that breakpoint cluster region-Abelson (BCR-ABL) mRNA was not detected in cord blood (Fig. 1) nor in the peripheral blood of the four-month-old baby (data not shown) as has been shown by Crump et al. [1], although aberrant transcripts were found in maternal blood at the time of the delivery. The woman continues to have chronic phase CML, and she remains on IFN-α therapy. Cytogenetic analysis using bone marrow cells revealed a decrease in the percentage of Ph-positive cells from 100% to 45%. The baby's growth and development have been normal to date (30 months).

Successful pregnancies and deliveries in CML patients have been reported using leukapheresis, IFN-α, or antineoplastic agents for control of the disease [2]. Leukapheresis rapidly reduces high leukocyte counts, but a risk of hemodynamic instability, which may be harmful to the pregnancy, exists. Busulfan and hydroxyurea can be used safely during pregnancy, but congenital malformations have been observed with busulfan therapy during pregnancy [3]. Neither teratogenic effects nor hematologic consequences to the fetus have been reported with hydroxyurea therapy [2]. However, both busulfan and hydroxyurea inhibit DNA synthesis, and may cause abortion, malformation, or fetal growth retardation. Stillbirths have been documented in patients on hydroxyurea therapy during pregnancy, although they could not be ascribed to the hydroxyurea therapy with certainty [4].

On the other hand, there are no reports of such serious complications in CML patients treated with IFN-α during pregnancy. This may be because IFN-α inhibits cell proliferation by effects on protein synthesis and on RNA degradation, rather than by inhibition of DNA synthesis. Another reason may be related to the finding that IFN-α2a cannot cross the placenta [5]. In our patient, the pregnancy proceeded without complication and the baby apparently had no congenital anomalies. IFN-α therapy may be safe for the treatment of CML during pregnancy.

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